UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/627,245 | 07/25/2003 | James A. Thomson | 960296.99179 | 4191 |

7590 12/31/2007

Nicholas J. Seay
Quarles & Brady LLP
P.O. Box 2113
Madison, WI 53701-2113

| EXAMINER | |
|---|---|
| SULLIVAN, DANIEL M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 12/31/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/627,245 | THOMSON ET AL. | |
| | Examiner | Art Unit | |
| | Daniel M. Sullivan | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3,7,9,10,12,13,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 7, 9, 10, 12, 13, 15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

This Office Action is a reply to the Paper filed 31 October 2007 in response to the Final Office Action mailed 11 July 2007. Claims 1, 3, 7, 9, 10, 12, 13, 15 and 16 were considered in the 12 December Office Action. Claims 1, 7, 10, 13 and 16 were amended 31 October Paper. Claims 1, 3, 7, 9, 10, 12, 13, 15 and 16 are pending and under consideration.

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 31 October 2007 has been entered.

### *Response to Amendment and Arguments*

Claim Objections

Objection to claims 7, 10 and 13 as containing informalities is withdrawn in view of the amendments thereto.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 7, 9, 10, 12, 13, 15 and 16 **stand rejected** under 35 U.S.C. 103(a) as being unpatentable over Priori et al. (1996) *Circ. Res.* 78:1009-1015 (the discussion herein below references the online publication, which is mailed herewith) in view of Gepstein et al. (*supra*; as evidenced by US provisional application 60/306,462). This rejection is maintained for the reasons set forth herein below and in the response to Applicant's arguments.

Independent claim 1 is directed to a method comprising deriving atrial-, ventricular- and nodal cardiomyocyte cell types after *in vitro* culture for between 40 and 95 days of embryoid bodies from human embryonic stem cells, piercing a single cardiomyocyte with an electrode, assessing the transmembrane action potential of the cardiomyocyte to characterize the cardiomyocyte as to the cell type of the human heart the action potential most resembles, exposing the cardiomyocyte to an agent, and observing whether the action potential of the cardiomyocyte changes after exposure to the agent.

Independent claim 7 comprises the steps recited in claim 1, recites that the electrode is inserted in to the interior of a single cardiomyocyte and further recites that the action potential is observed for a change in duration triggered by the agent.

Independent claim 13 comprises the steps of claim 1 and further comprises obtaining a chart of the transmembrane action potential of a plurality of the cardiomyocytes over time. The claim further recites that the system is observed for a long QT syndrome triggered by the agent.

Independent claim 16 comprises culturing human embryonic stem cells *in vitro* culture to produce embryoid bodies, selecting embryoid bodies that demonstrate the presence of atrial-, ventricular- and nodal cardiomyocyte cell types, piercing the embryoid body to place an electrode inside a single cardiomyocyte within the embryoid body and then practicing the measuring, assessing, exposing and observing steps as set forth in claim 1.

Priori et al. teaches a method comprising measuring the intracellular action potential of cardiomyocytes in culture by impaling the cardiomyocytes with an electrode. (See especially the first full paragraph on page 4 of 19, Figures 1-6 and the captions thereto.) Priori et al. further teaches exposing the cardiomyocytes to an agent and observing whether the action potential duration (APD) is changed after exposure. (See especially Figures 1-6 and the captions thereto.)

The method of Priori et al. also comprises assessing the transmembrane action potential of the cardiomyocyte. Although Priori et al. does not explicitly teach characterizing the cardiomyocyte as to the cell type of the human heart that the action potential most resembles, the step is inherent to the method of Priori et al. In paragraph 00021, the instant specification discusses action potential waveforms characteristic of atrial, ventricular and nodal cardiomyocytes and states, "These signals...are diagnostic of cell type to those knowledgeable in

the field of cardiac electrophysiology." (Emphasis added.) The characterization step in the instant claims is a purely mental act requiring only information as to the wave form of an action potential and knowledge as to the characteristics of atrial, ventricular and nodal wave forms. Priori et al. teaches a method wherein action potential wave forms are obtained (see especially Figures 2 and 4) and, because the authors of Priori et al. are clearly knowledgeable in the art of cardiac electrophysiology, the authors would recognize a given wave form as most closely resembling a ventricular, atrial or nodal cell. In other words, given that all of the information required to characterize the action potential as most resembling ventricular, atrial or nodal type was present in the mind of the authors, and the authors are knowledgeable in the field of cardiac electrophysiology, the skilled artisan would conclude, absent evidence to the contrary, that the step of characterizing occurred in the mind of the authors and is inherent to the method of Priori et al.

Thus, Priori et al. teaches a method comprising all of the limitations of the instant claims 1, 7 and 16 except for deriving cardiomyocytes in vitro from human embryonic stem cells.

In Figures 2 and 4, Priori et al. teaches a chart of the transmembrane action potential over time according to claims 10 and 13. Furthermore, throughout the publication Priori et al. teaches that action potentials were measured in a plurality of cardiomyocytes according to the limitations of claim 13. (See especially the second and third full paragraphs on page 5 of 19, the first paragraph on page 6 of 19, the first paragraph on page 7 of 19 and Figure 5.) Although Priori et al. does not explicitly teach that the cardiomyocytes were observed for delayed after polarization, the observing step of Priori et al. is the same as observing for delayed after polarization would be observed in the method of Priori et al. if the phenomenon is present. Therefore, Priori et al.

teaches a method comprising all of the limitations of claims 10 and 13 except for deriving cardiomyocytes from human embryonic stem cells.

Gepstein et al. teaches a method of culturing cardiomyocytes derived from human embryonic stem cells comprising permitting human embryonic stem cells to form embryoid bodies and then plating the embryoid bodies on 0.1% gelatin to induce differentiation. (See especially the section entitled "ES cell preparation and production of EBs" beginning on page 3 of the '462 provisional application.) Although Gepstein et al. does not explicitly teach that atrial-, ventricular- and nodal cardiomyocyte cell types are present, Gepstein et al. does teach a method of obtaining spontaneously beating cells having many properties of cardiomyocytes (see especially pages 7-10 of the '462 provisional application), wherein the method is is essentially the same as the method used in the working example of the instant application (i.e., gelatin coated plates in media comprising DMEM, FBS, L-glutamine, and non-essential amino acids; compare paragraph 00027 of the instant application to "ES cell preparation and production of EBs" of Gepstein et al. (*Id.*)). Furthermore, the ES cell line used by Gepstein et al. is identified as H9.2, which appears to be the same as the H9 cells used in the instant application. (See the first line of the second full paragraph on page 3 and reference 14 of Gepstein et al., which is a publication from the instant inventor's own laboratory.) Gepstein et al. further teaches maintenance of these cultures for up to 5 weeks. (See especially the final sentence in the second full paragraph on page 7.) Given the similar nature of the method used by Gepstein et al. to derive cardiomyocytes from cultured cells and the method used in the instant application to obtain cultures comprising atrial-, ventricular-, and nodal- cardiomyocyte cell types; given the vague description of atrial-, ventricular-, and nodal- type cardiomyocytes provided in the

specification[1]; and given the broad scope of the claims, which require that a given culture comprise only a single cell of each type, one of skill in the art would conclude, absent evidence to the contrary, that the cultures of Gepstein et al. comprise atrial-, ventricular-, and nodal-type cardiomyocytes as required by the claims.

With regard to the limitation that the derivation of cardiomyocytes is after *in vitro* culture for between 40 and 95 days, derivation within the recited range would also be obvious in view of the teachings of Gepstein et al. MPEP 2144.05 I. states, "[A] prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties." (Citing *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985).) In the instant case, Gepstein et al. teaches culturing embryoid bodies obtained from human ES cells under the same conditions used in the working example of the instant application. Gepstein et al. further teaches that the onset of spontaneously beating cells peaked at 11 days post plaiting and that cells continued to beat vigorously through the 35 days of the study. (See especially the second full paragraph on page 7.) In addition, Gepstein et al. shows that the appearance of beating cells reached a plateau after 20 days. (See especially Figure 2.) Given this information, one of skill in the art would expect that a process comprising culturing embryoid bodies for 40 days, the lower limit of the range recited in the instant claims, would have the same outcome as culturing cells under the same conditions for up to 35 days as described by Gepstein et al. Therefore, absent evidence to the contrary, a process comprising deriving cardiomyocyte cells

[1] See especially paragraph 00044 of the specification which relies on relative indicia such as "prominent phase-4 depolarization, slow upstroke and smaller APA" with no clear definition of the values of phase-4 depolarization, upstroke speed and APA size that defines a given cell as atrial-, ventricular-, or nodal-type.

after *in vitro* culturing for between 40 and 95 days of embryoid bodies from human embryonic stem cells is not patentably distinct from a process comprising deriving cardiomyocyte cells after *in vitro* culture for up to 35 days of embryoid bodies from human embryonic stem cells according to the method of Gepstein et al.

In the paragraph bridging pages 36-37 of the '462 application, Gepstein et al. teaches that the cardiomyocytes produced by the method "can be used as a testing system for evaluating the toxicity, teratogenicity and efficacy of new drugs and chemicals and thus may serve as an attractive screening tool with wide spread applications in the pharmaceutical industry" and "Using this system it is possible to study the short and long-term effects of drugs on pacemaker activity."

Thus, the teachings of Gepstein et al. demonstrate that a method of culturing cardiomyocytes comprising permitting human ES cells to form embryoid bodies was known in the art at the time the invention was made, and that these cells would be useful to evaluate the toxicity of new drugs and drug effects on pacemaker activity.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cardiomyocytes cultured according to the teachings of Gepstein et al. for the cardiomyocytes used in the method of Priori et al. and according to the limitations of the instant claims.

Motivation to combine the teachings of Priori et al. can be found in the nature of the problem to be solved by the method of Priori et al., which is to create an in vitro model to reproduce the alterations in long-QT syndrome patients for the purpose of testing interventions of potential clinical relevance. (See especially the "Abstract" lines 6-7 on page 1 of 19 and lines

7-9 on page 2 of 19. See also the "Conclusions" on page 11 of 19.) In view of this and the teachings of Gepstein et al. that "[t]he major advantage of this model is that it is the only existing long-term in vitro model for human tissue that is currently available", the skilled artisan would be motivated to use the cardiomyocyte culture system of Gepstein et al. to obtain the expected benefit of a long term human *in vitro* model, which would provide human cardiomyocytes for characterization of drugs to be used in humans and which would obviate the relatively difficult procedure of obtaining cardiomyocytes from guinea pigs taught in the method of Priori et al.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings in view of the demonstration by Gepstein et al. that the cardiomyocytes obtained according to the method described therein exhibit cardiomyocyte action potentials (see especially Figure 1 and the Figures on the final page (labeled 38(a)).

With regard to the limitations of claims 3, 9, 12 and 15, which require, "measuring includes impaling an embryoid body with an electrode", this limitation would be obvious in view of the fact that the method of measuring transmembrane action potential of Priori et al. comprises impaling a single cell with an electrode. As the cardiomyocytes cultured according to the method of Gepstein et al. are comprised in an embryoid body, contacting the cell with an electrode would comprise impaling the embryoid body comprising the cells.

For these reasons, the invention of the instant claims, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 U.S.C.§103(a) as obvious over the art.

*Response to Amendment and Arguments*

In response to the previous rejection of the claims as obvious over Priori et al. in view of Gepstein et al. Applicant has amended independent claims 1, 7, 10 and 13 to recite that after *in vitro* culture of embryoid bodies derived from human embryonic stem cells for between 40 and 95 days, atrial-, ventricular and nodal cardiomyocyte cell types are derived. Applicant asserts that at least this element of the claims is not reasonably predictable form the Gepstein et al. application. Applicant basis this assertion on the failure of Gepstein et al. to assess their cardiomyocytes and the distinctions between mouse and human development.

Applicant contends that Gepstein et al. cultured their embryoid bodies for no more than 30 days and stressed repeatedly the early nature of the cardiomyocytes in their cultured embryoid bodies. Applicant further contends that because Gepstein et al. do not explicitly disclose that the three recited cell types are present in the culture and pointed only to morphological differences among cells in the embryoid bodies. Applicant asserts that the skilled person cannot determine whether the early Gepstein et al. cardiomyocytes reflect differences that precede lineage specification, reflect differences within a single lineage after lineage specification, or reflect some other situation. Applicant concludes that because Gepstein et al. did not measure the action potential of individual cells, that application provides no basis for asserting the presence of distinct cardiomyocyte cell types, or even whether the given culture conditions would suffice to derive the recited cell types.

These arguments have been fully considered but are not deemed persuasive. First, with regard to claim 16, it is noted that the claim does not recite the limitations that Applicant contends distinguish the claimed invention from the prior art. With regard to the claims that do

recite those limitations, Applicant's position, in sum, is that the instant claims are not obvious over the teachings of the cited art because Gepstein et al. fails to provide explicit teaching of properties of the cultures that one of skill in the art would conclude are inherent.

First, Applicant is reminded, "There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference." (See MPEP 2112 II.) Furthermore, "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on 'inherency' under 35 U.S.C. 102, on 'prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald*, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)). See MPEP 2112 V.

As discussed above, Gepstein et al. teaches a method of obtaining spontaneously beating cells from embryoid bodies, maintenance of these cultures for up to 5 weeks, and that the cells obtained have many properties of cardiomyocytes. The method used by Gepstein et al. is essentially the same as the method used in the working example of the instant application (i.e., gelatin coated plates in media comprising DMEM, FBS, L-glutamine, and non-essential amino acids) and the ES cell line used by Gepstein et al. is identified as H9.2, which appears to be the same as the H9 cells used in the instant application. Given the similar nature of the method used by Gepstein et al. to derive cardiomyocytes from cultured cells and the method used in the instant application to obtain cultures comprising atrial-, ventricular-, and nodal- cardiomyocyte

cell types; given the vague definition of atrial-, ventricular-, and nodal- type cardiomyocytes provided in the specification, which essentially relies on the skilled artisan to decide that certain features of the action potential are more or less like one of the recited cardiomyocyte cell types; and given the broad scope of the claims, which only require that a given culture comprise a single cell of each type, one of skill in the art would conclude, absent evidence to the contrary, that the cultures of Gepstein et al. comprise atrial-, ventricular-, and nodal-type cardiomyocytes as required by the claims. In view of this, it is Applicant's burden to prove that the cells described by Gepstein et al. would not comprise at least one atrial-type cell, at least one ventricular-type cell and at least one nodal-type cell as those cells are generically defined in the instant application.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 USC § 103(a) as obvious over the art.

## *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel M Sullivan/
Primary Examiner
Art Unit 1636